Saudi Public Assessment Report

Divinusmet ®

Active Pharmaceutical Ingredient(s): Dapagliflozin, Metformin hydrochloride

ATC code/CAS no.: NA

Pharmaceutical/Dosage Form: Extended-release Tablets

Dosage Strength: 5 mg/1000 mg - 10 mg/1000 mg

Marketing Authorization Holder: Jazeera Pharmaceutical Industries

Shelf life: 24 Months and 1 month after first opening

Storage conditions: Do not store above 30°C

Registration No.: 0206210763, 0206210764

Decision and Decision Date: Approved on 12/03/2021

Table of Contents

1. Terms, Definitions, Abbreviations 3

2. Background 4

2.1 Submission Details 4

2.2 Regulatory Background 4

2.3 Product Information 4

3. Scientific discussion about the product: 4

3.1 Quality Aspects ..... **Error! Bookmark not defined.**

3.1.1 Drug Substance ..... **Error! Bookmark not defined.**

3.1.2 Drug Product 5

3.2 Clinical Aspects 6

3.2.1 Bioequivalence study 6

4. Risk Management Plan 9

5. Overall Conclusion 10

6. Appendix 11

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1. Terms, Definitions, Abbreviations

Terms	Definitions
AUC_{0-t}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time 0 to infinite time
C.I	Confidence Intervals
C_{max}	Maximum serum concentration
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
INN	International Nonproprietary Names
SFDA	Saudi Food and Drug Authority
SDI	Saudi Drug Information System
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics
USAN	United States Adopted Names

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2. Background

2.1 Submission Details

Type of submission: Human Generic Drug

Reference product in SRA: XIGDUO XR Film Coated Tablet

Pharmacological class: Antihyperglycaemic

Submitted Indication: Divinusmet (dapagliflozin/metformin extended-release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

Limitations of Use: Divinusmet XR is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

Submitted Dosage: 5 mg/1000 mg - 10 mg/1000 mg

2.2 Regulatory Background

This product is considered a human generic drug for Saudi regulatory purposes. Furthermore, this product qualified to follow the regulatory pathway normal submission.

2.3 Product Information

The officially approved Summary of Product Characteristics (SPC) can be accessed via Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

3. Scientific discussion about the product:

3.1 Quality Aspects

3.1.1 Drug Substance

Dapagliflozin Propanediol Monohydrate:

- Dapagliflozin propanediol monohydrate is a white to off-white powder. Dapagliflozin propanediol monohydrate is soluble in methanol and practically insoluble in cyclohexane and water. Dapagliflozin propanediol monohydrate does have six chiral centers. Polymorphism has been observed.

- The drug substance is manufactured by a multiple-step chemical synthesis.
- The structure of Dapagliflozin Propanediol Monohydrate has been fully elucidated using several spectroscopic techniques.
- The drug substance specification includes relevant tests for proper quality control. The control methods are validated according to international guidelines.
- Appropriate stability data have been presented and justify the established re-test period.

Metformin Hydrochloride:

- Metformin Hydrochloride is white free flowing granules. Metformin Hydrochloride is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride. Metformin Hydrochloride does not have any chiral centers. Polymorphism has been observed.
- The drug substance is manufactured by a multiple-step chemical synthesis.
- The structure of Metformin Hydrochloride has been fully elucidated using several spectroscopic techniques.
- The drug substance specification includes relevant tests for proper quality control. The control methods are validated according to international guidelines.
- Appropriate stability data have been presented and justify the established re-test period.

3.1.2 Drug Product

- The drug product is available in two strengths:

1. 5/1000 mg extended-release tablets: Pink, capsule modified shaped film coated tablet engraved with WW89 on one side, partial bisected.
2. 10/1000 mg extended-release tablets: Yellow, capsule modified shaped film coated tablet engraved with WW89 on one side, partial bisected.

- Each tablet contains 5 mg or 10 mg of Dapagliflozin and 1000 mg of Metformin Hydrochloride. The composition of the drug product is adequately described, qualitatively and quantitatively. Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
- The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
- The drug product specification covers appropriate parameters for this dosage form, which allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
- The drug product is packaged in a carton box, containing a white HDPE round bottle with child resistance white caps with aluminum seal and liner, with 2 g desiccant bag, containing 30 extended-release tablets.
- Appropriate stability data have been generated in the packaging material intended for commercial use and following relevant international guidelines. The data show good stability of the finished product and support the shelf life.

3.2 Clinical Aspects

3.2.1 Bioequivalence study

Bioequivalence study (under fasting condition):

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Divinusmet® (Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride) 10/1000 mg of Hikma Pharmaceuticals, Jordan and Xigduo XR® (Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride) 10/1000 mg of AstraZeneca pharmaceuticals, USA, in healthy human adult subjects, under fasting conditions. The study was conducted in accordance with (GCC) Guidelines for

Bioequivalence, standards of Good Clinical Practice (GCP) and Good Laboratory Practices (GLP).

Blood samples were taken pre-dose (0.0) and at a specified time points up to 48 hours after administration of test or reference product. Plasma levels of Dapagliflozin and Metformin were detected by a validated LC-MS/MS method.

Thirty (30) volunteers completed the study and all data were analyzed. No significant protocol deviations were reported. There were no serious adverse events reported in the study.

The ratio and 90% Confidence Intervals of Test versus Reference for Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride are tabulated below:

Table 1: Ratio and 90% Confidence Intervals (C.I) of Test versus Reference for Dapagliflozin:

Pharmacokinetic Parameter	**Point Estimate**	**90% Confidence Intervals (%)**
C_{max}	100.31	93.22 – 107.93
AUC_{0-t}	105.18	102.38 – 108.06
$AUC_{0-\infty}$	104.13	101.63 – 106.68

Table 2: Ratio and 90% Confidence Intervals (C.I) of Test versus Reference for Metformin:

Pharmacokinetic Parameter	**Point Estimate**	**90% Confidence Intervals (%)**
C_{max}	108.41	99.62 – 117.97
AUC_{0-t}	109.18	101.99 – 116.87
$AUC_{0-\infty}$	108.38	101.72 – 115.47

Bioequivalence study (under fed condition):

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Divinusmet® (Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride) 10/1000 mg of Hikma Pharmaceuticals, Jordan and Xigduo XR® (Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride) 10/1000 mg of

AstraZeneca pharmaceuticals, USA, in healthy human adult subjects, under fed conditions. The study was conducted in accordance with (GCC) Guidelines for Bioequivalence, standards of Good Clinical Practice (GCP) and Good Laboratory Practices (GLP).

Blood samples were taken pre-dose (0.0) and at a specified time points up to 48 hours after administration of test or reference product. Plasma levels of Dapagliflozin and Metformin were detected by a validated LC-MS/MS method.

Thirty (30) volunteers completed the study and all data were analyzed. No significant protocol deviations were reported. There were no serious adverse events reported in the study.

The ratio and 90% Confidence Intervals of Test versus Reference for Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride are tabulated below:

Table1: Ratio and 90% Confidence Intervals (C.I) of Test versus Reference for Dapagliflozin:

Pharmacokinetic Parameter	**Point Estimate**	**90% Confidence Intervals (%)**
C_{max}	102.50	88.79 – 118.33
AUC_{0-t}	98.46	96.25 – 100.73
$AUC_{0-\infty}$	96.88	94.61 – 99.22

Table 2: Ratio and 90% Confidence Intervals (C.I) of Test versus Reference for Metformin:

Pharmacokinetic Parameter	**Point Estimate**	**90% Confidence Intervals (%)**
C_{max}	98.02	92.87 – 103.46
AUC_{0-t}	96.11	90.29 – 102.31
$AUC_{0-\infty}$	96.22	90.43 – 102.37

Based on the results obtained in these studies, Divinusmet® (Dapagliflozin Propanediol Monohydrate / Metformin Hydrochloride) 10/1000 mg of Hikma Pharmaceuticals, Jordan is **bioequivalent** to Xigduo XR® (Dapagliflozin Propanediol Monohydrate / Metformin

Hydrochloride) 10/1000 mg of AstraZeneca pharmaceuticals, USA under fasting & fed conditions.

4. Risk Management Plan

4.1 Artwork and Trade Name assessment (Artwork available in appendix)

Proposed trade Name	Dosage Form
Divinusmet	Extended-release Tablets

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

Divinusmet name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN International Nonproprietary Names and USAN United States Adopted Names STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Divinusmet	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Divinusmet is accepted.

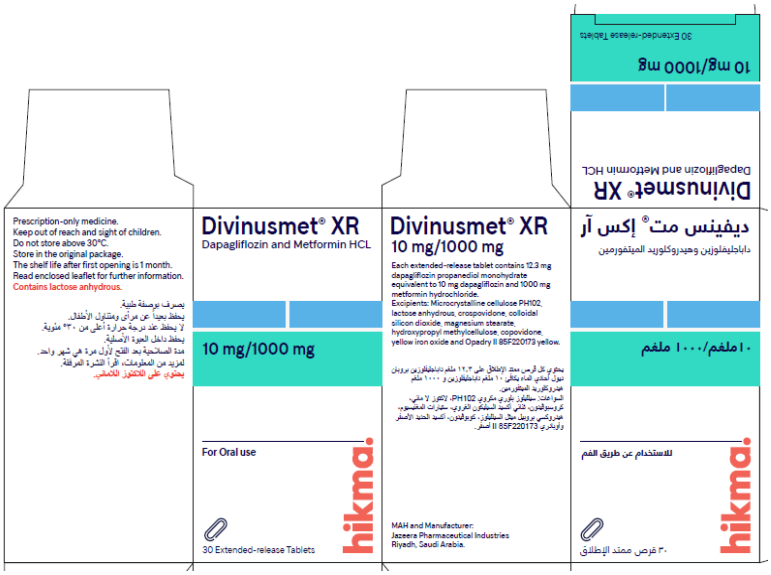
Outer and Inner Package:

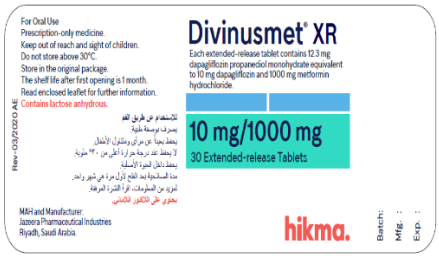
Based on the submitted data, the proposed artwork is accepted.

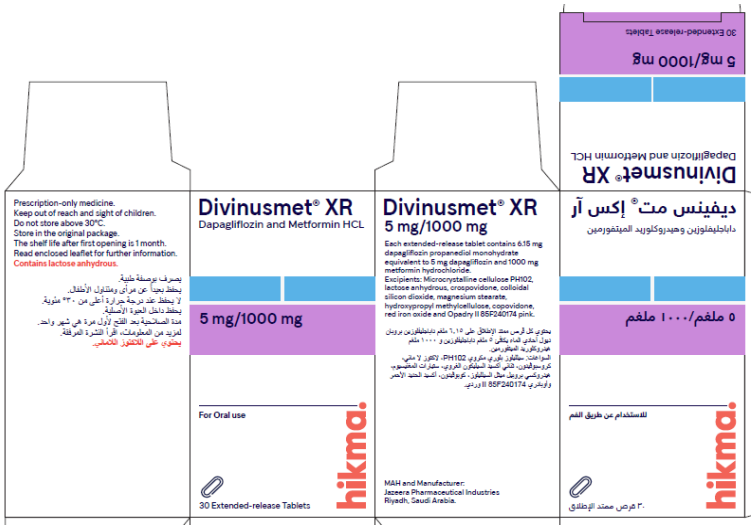
5. Overall Conclusion

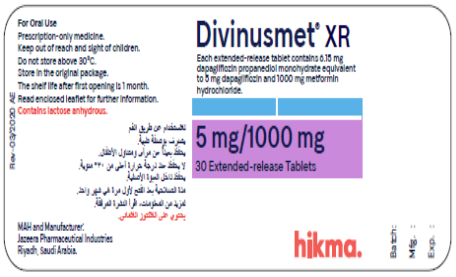
Based on data reviewed from quality, safety and efficacy, prospective. The SFDA considered that the benefit/risk profile of Divinusmet XR was favorable and decided to grant the marketing authorization of Divinusmet XR used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

6. Appendix









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The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published only at SDI.

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa